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# Changing Views: The Emergence and Efficacy of Natural Hormones in the Treatment of Menopause

Deborah Moskowitz, ND

Managing Physician, Transitions For Health, Inc., Portland, Oregon

Adjunct Professor of Clinical Research, National College of Naturopathic Medicine, Portland, Oregon

## INTRODUCTION

Women in increasing numbers are asking their physicians for natural hormone replacement therapy (nHRT) for treatment of symptoms at menopause as well as prevention or risk reduction for osteoporosis and heart disease.<sup>1</sup> Numerous factors contribute to this trend, including a movement toward “natural” therapies and a fear or suspicion of “synthetic” drugs. This movement, which has gained significant ground in the eighties and nineties, follows closely on the heels of the natural foods movement, that blossomed in the sixties. It also corresponds temporally with the establishment of groups promoting less medical intervention with respect to natural human functions such as childbirth and lactation (ie La Leche League, midwifery groups). Recent media reports of risks associated with conventional hormone replacement therapy (HRT) have further prompted women’s concerns.<sup>2-3</sup>

## HORMONE CHANGES SURROUNDING NATURAL (NON-INDUCED) MENOPAUSE

Menopause is defined as the cessation of menstruation that occurs as a result of the loss of ovarian follicular activity. At birth, a woman has close to a million eggs, by

puberty a mere 300,000. As a result of the decreasing follicles, FSH (follicle-stimulating hormone) levels gradually increase and the cycle begins to shift, with a shortening of the follicular phase that can begin as early as a woman’s 20’s.<sup>4-5</sup> In the 10 to 15 years prior to menopause, this rate of follicular atresia begins to accelerate.<sup>6-7</sup> Perimenopause is the term used to describe the time of transition between a woman’s reproductive years and when menstruation ceases completely. Typically perimenopause occurs between the ages of 40 and 51 and may last anywhere from six months to ten years. During this time, hormone levels naturally fluctuate and decline, do not necessarily in an orderly manner.

Perimenopause is often heralded by an alteration in cycle and bleeding regularity due to fluctuating hormones, anovulatory cycles, and changes in timing of ovulation. Cycles may be long or short, ovulatory or anovulatory.<sup>7</sup> Even women who are cycling regularly during this period can have a significant variability in the level of hormones.<sup>6</sup> Progesterone levels drop with anovulatory cycles and a decline in luteal function. Estrogen levels fluctuate in response to rising FSH levels, as well as provide feedback inhibition to FSH.<sup>5</sup> Significant variability may be seen in estradiol and inhibin, and gonadotropins may rise abruptly.<sup>4-5,8</sup> Testosterone levels decline with age and do not appear to change significantly with natural menopause. By menopause, few follicles remain, yet intermittent estradiol production from the ovaries may still occur.<sup>7-8</sup> Post-menopausally, adrenal androstenedione is the primary source of estrogen. Serum testosterone falls slightly, as well as sex-hormone-binding globulin.<sup>9</sup> FSH levels remain high for several years after menopause, after which levels decline considerably.<sup>9-10</sup>

### \*Correspondence:

Deborah Moskowitz, ND  
621 SW Alder, Suite 900  
Portland, Oregon 97205  
Phone: 800-648-8211 Ext. 139 Fax: 800-944-0168  
E mail: dmoskowitz@progest.com

Although FSH is commonly used, there are no consistent reliable endocrine markers to establish a woman's menopausal status.<sup>8</sup> Shifts in hormones are a major contributor to that sense of physical, mental, and emotional imbalance that may characterize a woman's experience of menopause. As a clinician, it is important to note the changes that occur, link them to the physiology of the various hormones, and address imbalances individually. Addressing other aspects of endocrine health is also necessary and may involve assessing adrenal fatigue or stress, liver function and other routes of hormone elimination, as well as diet, exercise, and other lifestyle factors.

### PROBLEMS WITH CONVENTIONAL HRT

Although HRT has established benefits for the treatment of menopausal complaints as well as a reduction in bone loss and some beneficial effects on the heart, relatively few women who may benefit from HRT choose or intend to use it.<sup>11-13</sup> Additionally, women who are prescribed HRT often discontinue it before long-term benefits are realized. The most common reason for discontinuation of HRT is unwanted side effects and weight gain, with one-third to two-thirds of women initiating HRT discontinuing it within the first two years.<sup>11-12,14-16</sup> Most side effects were attributed to the progestin portion of HRT, with the most common complaints being bloating, breast tenderness, and irregular bleeding.<sup>11,12,17</sup> Secondary reasons for discontinuation included fear of cancer and recommendation by a physician. For women not initiating HRT, reasons cited included: failure to see the need for hormone replacement, a preference to not to take medications, a fear of the effects of long-term HRT, confusion over the scientific information as presented in the media, and the view that menopause is a natural event.<sup>2,3,12,18</sup> Use of HRT was correlated with older women's wishes to reduce osteoporosis risk, while younger women sought relief from menopausal symptoms, predominantly vasomotor flushing.<sup>2,17</sup> Given this information, it should follow that utilizing hormones that have fewer side effects and risks fit with a woman's perception of "natural", and addressing long-term health benefits could increase hormone use and therefore a woman's health and well-being at and beyond menopause. Reviewing existing research, natural hormones may fit the bill.

### WHAT IS "NATURAL" HRT (nHRT)?

There is much confusion over the term "natural", and according to Webster's Dictionary, natural can refer to something that is "usual" or "customary", of which the conventional practice of HRT certainly fits. Let us, then, for our purposes define natural hormones as those that are identical to hormones produced endogenously by our bodies, or "bio-identical". In nHRT, these would include estradiol (E2), estrone (E1), estriol (E3), and progesterone (P4). Although

bio-identical hormones have long been utilized in other countries, the United States has predominately used non-bio-identical hormones in the last 50 years, beginning with the introduction of oral contraceptives in the early 1960s.

### HOW ARE BIO-IDENTICAL HORMONES DIFFERENT?

The differences in the actions, risks, and benefits of various hormones depend on numerous factors, including method of administration, absorption, bioavailability, metabolism, receptor affinity, receptor specificity, and molecular structure.<sup>19,25</sup>

### NATURAL VERSUS SYNTHETIC ESTROGENS

The body naturally produces three main forms of estrogen: estrone (E1), estradiol (E2), and estriol (E3). Synthesized in the ovaries and metabolized in the liver, estradiol is the most physiologically active form of estrogen. When taken orally, estradiol is converted into estrone in the small intestine. Increased serum estradiol levels are linked to an increased risk of breast and endometrial cancer.<sup>26</sup> Estrone is converted from estradiol in the liver. Estrone increases after menopause when the adrenal glands play a more prominent role in hormone synthesis than do the ovaries. Estriol is considered the "weakest" estrogen, as it has a shorter-acting effect than estradiol and estrone.<sup>27</sup> However, depending on sufficient dosing and route of application, estriol can attain a full estrogenic effect on target tissue.<sup>27</sup> Estriol remains intact when supplemented orally (i.e. estriol is *not* converted into estrone, as occurs with estradiol supplementation).<sup>28</sup> In Europe and China estriol is commonly used for HRT. A comprehensive review of the safety and efficacy of estriol suggests that it may be safer than estrone or estradiol, but can still have a stimulatory action on the endometrium and the breast when given in high doses.<sup>29</sup>

The predominant estrogen currently prescribed in the United States is Premarin®, a brand of conjugated equine estrogens. Premarin® contains close to a hundred distinctly different estrogens, mainly estrone sulfate, equillins, equilinins, and alpha estradiol, all of which are estrogens that occur naturally in horses, with few natural to the human body. Many estrogen formulations presently available in the United States contain bio-identical estrogens (Table 1). A growing number of complementary and alternative (CAM) physicians are now prescribing "Tri-Est", or "Bi-Est", nicknames given to individually- compounded formulations of estriol, estrone, and estradiol or estriol and estradiol respectively. Licensed pharmacists may compound these combinations of natural estrogens in a variety of doses and delivery systems.

## NATURAL PROGESTERONE VERSUS SYNTHETIC PROGESTINS

An inconsistency in the use of the terms “progesterone”, “progestin”, and “progestogen” has led to confusion over these substances. *Progesterone* refers to a single (note the “one” at the end of the term) molecular structure that is identical to the progesterone molecule that the body makes, or P4. *Progestogen* is the category of hormone molecules (natural and synthetic) that act like progesterone in the uterus. *Progestin* is generally used to refer to synthetic progestogens. Originally progesterone was procured by methods of extraction from animal placenta. Natural progesterone products today are produced in a laboratory setting via a process designated as the “Marker Degradation” from saponins found in soy and wild yam (*Dioscorea villosa*). Hudson (1996) presents a detailed historic perspective of the series of events surrounding the discovery of this process.<sup>30</sup>

Progesterone was first used as HRT in 1934 for the treatment of ovariectomized women.<sup>21</sup> Due to significant first-pass effect of progesterone, synthetic progestins were developed in the 1940s, either from progesterone (e.g. medroxyprogesterone acetate) or from testosterone (e.g. 19-nortestosterone).<sup>31</sup> Progestins mimic the body’s progesterone closely enough to bind to progesterone receptor sites, but they do not deliver the full range of “messages” that a natural progesterone molecule would. A synthetic progestin, for example, may have similar effects on the endometrium, yet can initiate widely different actions elsewhere in the body (i.e. brain, gonadotropins, mineralcorticoid receptors, etc.) depending on the classification of the particular progestin (nor-testosterone derivatives, ethyl 13 derivatives, progesterone derivatives, or nor-progesterone derivatives).<sup>32-33</sup> These different progestins have been mapped as to their affinity to androgen, progesterone, glucocorticoid, and estrogen receptors.<sup>24</sup> In contrast to progesterone, 19-nortestosterone derivatives are known to have estrogenic properties, which could be attributed to their estrane structure, or to the production of estrogen as a metabolite.<sup>34</sup> 19-nortestosterone derivatives have been shown to increase the growth of ER+ breast cancer cells in vitro.<sup>35</sup> A paper published this year discussed the development of newer synthetic progestins that more closely fit the profile of bio-identical progesterone.<sup>36</sup> What could be closer to progesterone than progesterone itself?

### ERT, PRT, OR HRT?

Current conventional standard of care (per ACOG) recommends that estrogens be prescribed in conjunction with progestins when a woman has an intact uterus; conversely, unopposed estrogens are the norm post-hysterectomy. Although progesterone and estrogen receptors both exist in tissues outside the uterus, it has not been thought necessary to provide progestins after the uterus is removed. In con-

trast, when using natural hormones, many CAM physicians consider the concomitant use of progesterone with estrogen replacement an important aspect of nHRT and hormonal balance. The growing research on the synergism of these two hormones, as well as an expanded understanding of progesterone’s effects in the body, are prompting some to recommend that these hormones be prescribed in conjunction, regardless of the presence or absence of a uterus.<sup>37-38</sup> When considering estrogen replacement during the perimenopause and early menopause, one must also consider the level of endogenous estrogen production, for even as FSH levels climb, this may be associated with an increase in estrogen, as opposed to a decrease in estrogen, as previously expected.<sup>8,10</sup> Since progesterone levels can fall first perimenopausally with the advent of anovulatory cycles, some women may do well with progesterone-only supplementation (PRT) at this time. This may help balance the effects of unopposed endogenous estrogen production. FSH, although commonly used as a diagnostic indicator of menopause, may not be the most reliable tool for determining estrogen needs perimenopausally.<sup>8</sup> One should also note that women with a greater amount of body fat can produce a significant amount of endogenous estrogen post-menopausally. This can occur exclusively through aromatization of estrogens from adrenal androstenedione by the fat cells.<sup>9</sup> In one study, 10-15% of women post-menopause produced enough estrogen to build the endometrial lining, further emphasizing the need to determine individually the potential hormonal needs of each woman during the climacteric.

### HORMONE SYNERGY

Hormone function can be affected by the presence of other hormones, as is seen in the synergistic effects of E2 and P4.<sup>37,39</sup> Even the receptors themselves can exhibit synergism, although the exact mechanisms are not fully elucidated.<sup>40,41</sup> An example of this phenomenon that has served well in clinical practice is the synergistic antiovarian effects of estrogen and progestogens that resulted in the use of lower dose oral contraceptives with efficacy equal to that of higher dose regimens. More recently, estradiol in combination with progesterone inhibited bone resorption to a greater degree than either hormone alone.<sup>42</sup>

### CONTINUOUS VERSUS PULSED DELIVERY

There is sufficient evidence to suggest that the pulsatile delivery of estrogen and progesterone that occurs naturally serves to enhance the functioning of these hormones in the body.<sup>43-45</sup> In theory, continuous application of hormones may serve to down-regulate receptors, contributing to a general decrease in the activity of those particular hormones. Research

has demonstrated that sequential pulsed estrogen and progestin therapy allows for smaller amounts of hormones to be used.<sup>43</sup> Reduced dosage would translate to reduced likelihood of unwanted side effects as well as a reduced impact on the liver metabolism by supplemented hormones.

## DIFFERENCES IN DELIVERY OF NATURAL HORMONES

Many different routes of delivery are available for natural hormones, including oral, transdermal (patch), percutaneous (cream, gel), IM, subcutaneous, sublingual, vaginal (gels, cream, tablet, ring, and pessary), and nasal. The route of administration can confer differences related to absorption, metabolic pathway engaged, and bioavailability. In general, the oral route leads to more rapid metabolism and a greater impact on hepatic processes, requiring greater oral doses than those by-passing the entero-hepatic circulation. With identical dosing for both oral and vaginal preparations, both progesterone and estradiol, when delivered vaginally, led to greater circulating blood levels than oral administration due to entero-hepatic metabolism.<sup>46</sup> In comparisons of different delivery systems of E2, percutaneous, transdermal, and vaginal delivery resulted in a reduction in metabolism to E1 via the entero-hepatic circulation.<sup>46-48</sup> Side effects common with oral E2 were not seen in percutaneous or transdermal routes.<sup>49-50</sup>

Approximately 90% of oral progesterone is metabolized by the "first pass effect" of the entero-hepatic circulation, leading to difficulties in dosing as well as an abrupt increase in 5-alpha progesterone metabolites.<sup>51</sup> Oral progesterone administration resulted in higher progesterone metabolites (deoxycorticosterone, deoxycorticosterone sulfate, and 5-alpha and beta pregnanolone) when compared to vaginal administration.<sup>46-52</sup> In a comparison with vaginal administration, similar endpoints were achieved with 300 mg oral micronized progesterone (OMP) and 90 mg vaginal progesterone, with fewer side effects of drowsiness noted with the vaginal application, an effect attributed to 5 alpha and beta metabolites of progesterone.<sup>53</sup> It is important to note that progesterone and its metabolites have differing effects in the brain, uterus, smooth muscle, and oocyte.<sup>54</sup> For example, depressive effects of progesterone are predominately attributed to pregnane metabolites, as opposed to progesterone itself. Given the increase in metabolites that are seen with oral micronized progesterone (OMP), vaginal or topical delivery systems may reduce expression of side effects attributed to these metabolites.

Because numerous factors can influence intestinal absorption and metabolism, oral preparations may be more variable in end effects. In a study of the pharmacokinetics of oral vs. IM administration of E2, 4 mg IM had a depot effect over 2-4 weeks that was equivalent to the oral administration of 2 mg daily over 3 weeks.<sup>55</sup> Oral micronized

progesterone (OMP) application exhibited substantial variability in absorption between individuals.<sup>56</sup> In a separate study, percutaneous absorption of a progesterone (P4) cream sustained only moderate variability between individuals.<sup>57</sup>

The base of a cream, gel, or suppository can also affect absorption.<sup>58-59</sup> In a study of topical applications, progesterone in a hydrophilic gel, lipophilic base, and emulsion type base all resulted in slower elimination when compared to vaginal.<sup>58</sup> Of the three topical bases used, the emulsion type base led to a greater area under the curve (AUC) and peak plasma concentration than either the hydrophilic gel or lipophilic base.<sup>59</sup>

A novel administration of progesterone via a nasal spray was successful in reaching physiological levels of serum progesterone.<sup>60</sup> Also unique was an effervescent progesterone vaginal tablet that resulted in adequate serum progesterone levels. In this study, there was a significant age-related difference in Tmax, with women over 40 years attaining a lower Tmax than younger women.<sup>61</sup>

Given the differences that abound in both the type and route for administration of hormones, physicians are urged to individually assess a patient's need for HRT and tailor the regime to the woman's needs and desires.<sup>25</sup>

## NATURAL HORMONES AND THE CARDIOVASCULAR SYSTEM

Hormones have multiple effects on the cardiovascular system, including eliciting actions on blood pressure, vascular tone, hemostasis, lipid metabolism, cardiac vasospasm, and glucose metabolism.

Progesterone has a natriuretic effect unlike synthetic progestins. This effect on sodium loss has been shown to reduce blood pressure in some studies, as well as ease symptoms of water retention.<sup>62-65</sup> Progesterone possesses anti-mineralocorticoid effects not seen with the majority of available synthetic progestins; moreover, some of these synthetic progestins exhibit an estrogenic effect, increasing potential for BP elevation.<sup>64-65</sup>

Progesterone can decrease sympathetic vascular tone, without concomitant drop in blood pressure.<sup>66</sup> Endogenous and low-dose parenteral E2 increase vasodilatation.

Whereas some synthetic progestins are known to exert a negative effect on blood lipids, natural progesterone does not appear to do so. In the PEPI trial progesterone (OMP) fared significantly better than MPA, as it didn't blunt the beneficial effects ERT had on HDL elevation.<sup>67</sup> This was also found in an earlier study comparing progesterone with both nortestosterone and MPA.<sup>68</sup> Third generation progestins, such as norgestimate and desogestrel have not demonstrated an adverse effect on serum lipids. It should be noted that synthetic progestins retain undesirable effects on liver metabolism even when administered through the skin.<sup>69</sup> Natural

progesterone, in both oral and vaginal administrations, has been demonstrated to be safe in its effects on lipid metabolism.<sup>70</sup> In a comparison between orally administered ethinyl estradiol (EE) and E2, both showed beneficial effects on serum lipids (EE>E), however, EE demonstrated a marked increase in liver protein synthesis.<sup>71</sup>

ERT is known to increase the risk of blood clots. High dose estrogens, especially synthetic estrogens, increase both protein synthesis via the liver and coagulation factors. They also increase SHBG and angiotensin, and may raise BP and stroke risk in susceptible women.<sup>64</sup> In a randomized crossover study, estriol did not affect hemostatic func-

**Table 1**

<b>ESTROGENS</b>	<b>BRANDS</b>
<b>Bio-Identical</b>	
17-beta estradiol (E2)	Alora <sup>®</sup> , Climera <sup>®</sup> , Estraderm <sup>®</sup> , Fempatch <sup>®</sup> , Oesclim <sup>®</sup> , Vivelle <sup>®</sup> (all E2 patches); Combi Patch <sup>®</sup> (E2 + norethindrone), Emcyt <sup>®</sup> (capsule), Estrace <sup>®</sup> (vaginal cream and tablet), Estring <sup>®</sup> (vaginal ring), available generically in a cream, gel, or capsule from compounding pharmacies
Estrone sulfate (E1)	Available generically in a cream or gel from compounding pharmacies
Estropipate (E1)	Ogen <sup>®</sup> (tablet and vaginal cream), Ortho-Est <sup>®</sup> (tablet), generic tablet
Estriol (E3)	Available generically in a cream or gel from compounding pharmacies
<b>Non-Bio-Identical</b> Ethinyl estradiol	Brevicon <sup>®</sup> , Demulen <sup>®</sup> , Levlen <sup>®</sup> , Lo-Ovral <sup>®</sup> , Loestrin <sup>®</sup> , Modicon <sup>®</sup> , Nordette <sup>®</sup> , Norinyl <sup>®</sup> , Ortho-Cept <sup>®</sup> , Ortho-Cyclen <sup>®</sup> , Ortho-Novum <sup>®</sup> , Ortho-Tri-Cyclen <sup>®</sup> , Ovcon <sup>®</sup> , Tri-Levlen <sup>®</sup> , Tri-Norinyl <sup>®</sup> , Triphasil <sup>®</sup> , Nelova <sup>®</sup> (all tablets in combination with synthetic progestins); Estinyl <sup>®</sup> (tablet), Feminone <sup>®</sup> (tablet)
Esterified estrogens	Estratab <sup>®</sup> (tablet), Menest <sup>®</sup> (tablet), Menogen <sup>®</sup> (tablet in combination with methyltestosterone)
Conjugated equine estrogens (CEE)	Premarin <sup>®</sup> (tablet, vaginal cream), PremPro <sup>®</sup> (tablet in combination with MPA), PremPhase <sup>®</sup> (tablet in combination with MPA), generic (tablet)
Dienestrol	Ortho Dienestrol Cream <sup>®</sup> (vaginal cream)
<b>PROGESTINS</b>	
<b>Bio-Identical</b>	
Progesterone (P4)	Crinone <sup>®</sup> (vaginal gel), Pro-Gest <sup>®</sup> (body cream), Prometrium <sup>®</sup> (capsule), available generically in a cream, gel, trochee, vaginal suppository, IM injectable, or capsule from compounding pharmacies
<b>Non-Bio-Identical</b>	
Medroxyprogesterone acetate (MPA)	Provera <sup>®</sup> (tablet), Amen <sup>®</sup> (tablet), Curretab <sup>®</sup> (tablet), Cycrin <sup>®</sup> (tablet), PremPro <sup>®</sup> (tablet in combination with CEE), PremPhase <sup>®</sup> (tablet in combination with CEE)
Norethindrone acetate	Aygestin <sup>®</sup> (tablet), Micronor <sup>®</sup> (tablet), Norlutate <sup>®</sup> (tablet), Nor-QD <sup>®</sup> (tablet)
Norethindrone	Norlutin <sup>®</sup> (tablet)
Norgestrel	Ovrette <sup>®</sup> (tablet)
Norgestimate	Ortho-Tri-Cyclen <sup>®</sup> (tablet in combination with EE)
Levo-Norgestrel	Preven (tablet in combination with EE)
Desogestrel	Desogen <sup>®</sup> (tablet)
Megestrol acetate	Megace <sup>®</sup> (tablet)

tion, whereas ethinyl estradiol (EE) decreased prothrombin time while increasing plasminogen and factor VII.<sup>72</sup>

MPA increases the extent of atherosclerosis on coronary arteries, suppresses the protective effect of estrogen on arterial injury, increases insulin resistance, and attenuates the beneficial effects of estrogen on vasodilatation.<sup>73-75</sup> This is consistent with findings that synthetic estrogen as well as 19-nortestosterone can result in a decrease in glucose tolerance, whereas glucose metabolism is unaffected by P4.<sup>76</sup>

In a study comparing E2 + P4 with E2 + MPA, E2 + P4 protected against coronary hyperreactivity and subsequent coronary vasospasm, whereas coronary vasospasm was increased in monkeys receiving MPA.<sup>77-78</sup>

Seventeen beta estradiol and progesterone both inhibited cardiac fibroblast growth, with the effects of 17 beta estradiol enhanced by P4, suggesting that the combination may help protect postmenopausal women against CV disease.<sup>79</sup>

### NATURAL HORMONES AND THE BREAST

The effect of synthetic progestins on the breast is unclear. Whereas progestins have been used historically to treat some forms of advanced breast cancer, a recent re-evaluation of results of a cohort study suggested an increased risk in the occurrence of breast cancer in women who were on combined HRT (predominately CEE + MPA) beyond that seen with unopposed estrogen. This risk increase was not statistically significant.<sup>80</sup> Other reports suggest a protective effect of progesterone and progestins.<sup>81-88</sup>

Although estrogens are generally perceived to be contraindicated for women at risk for breast cancer, there is considerable theoretical reason to believe that estriol in low doses could be protective for the breast.<sup>28,89-91</sup>

### NATURAL HORMONES AND THE ENDOMETRIUM

Both OMP and vaginal delivery of progesterone have resulted in sufficient end-organ effect on the uterus with doses beginning at 100 mg daily x 25 days/month and 45 mg qod for 6 doses/month respectively.<sup>69,92-93</sup> Similar end-organ results have been seen using percutaneous progesterone cream.<sup>94</sup>

### NATURAL HORMONES AND MENOPAUSAL SYMPTOMS

Although most physicians will attribute vasomotor flushing to a lack of estrogen, progestins can have a beneficial effect.<sup>95</sup> A recent study using a progesterone cream applied to the skin resulted in a significant reduction in the number and intensity of hot flashes in 83% of the study participants, as well as benefits in other quality of life measurements.<sup>96</sup>

Oral and transdermal estradiol preparations have been found to confer benefit for menopausal symptoms and vaginal cytology, as well as reduce bone loss in postmenopausal women.<sup>48,50</sup> Estriol has also been demonstrated to reverse vaginal atrophy.<sup>97-98</sup> Estriol doses must be increased up to three times the dose of estradiol to achieve similar effects (eg, reducing hot flashes and vaginal dryness in menopausal women) and is typically dosed twice daily to achieve steady blood levels.<sup>28</sup>

### NATURAL HORMONES AND BONE

Bone turnover increases at menopause and may remain high for over 25 years following the last menstrual cycle.<sup>99</sup> Hormonal control of bone turnover is not limited to a single hormone, but rather the complex interrelationship of a number of steroid and other hormones, including estrogen, progesterone, testosterone, corticosteroids, vitamin D, thyroid hormones, and retinoids.<sup>100</sup> When given alone, estrogens have a known beneficial effect on limiting bone loss as well as reducing the number of fractures. Studies with progesterone alone are favorable, but mixed. Several animal and human studies have demonstrated a clear positive effect on bone formation as well as inhibition of bone resorption,<sup>101-104</sup> although double-blind placebo-controlled studies in humans have yet to demonstrate a significant increase in BMD or a reduction in fracture rate. One short-term human study of OMP showed no difference in markers of bone resorption as compared to placebo.<sup>105</sup> Longer studies evaluating BMD and fracture rate are needed to determine the value of progesterone supplementation alone for preventing or treating osteoporosis. Several studies looking at estrogen and progesterone supplementation have suggested that both estrogen and progesterone have distinct and complementary roles in the maintenance of bone.<sup>42,104,106</sup> Testosterone has also been seen to decrease urinary calcium loss and bone resorption.<sup>107-108</sup>

### SUMMARY

The use of nHRT is well tolerated, provides symptom relief, and can address many of the health needs as well as the individual preferences of menopausal and perimenopausal women. Physicians are encouraged to take the time and effort to help women determine the regime that best suits their needs. This effort will undoubtedly pay off in fewer unwanted side effects and greater quality of life.

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